



DEPARTMENT OF HEALTH & HUMAN SERVICES

m4020n

Food and Drug Administration
466 Fernandez Juncos Avenue
Puerto De Tierra
San Juan, Puerto Rico 00901-3223

July 31, 2000

WARNING LETTER

SJN-00-20

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Patrick J. Zenner
President & CEO
Hoffman-LaRoche, Inc.
340 Kingsland St.
Nutley, NJ 07110-1199

Dear Mr. Zenner:

From May 10 to July 23, 1999, and from September 15 to 29, 1999, an investigator from our office conducted inspections of your drug manufacturing facility, Roche Pharma, Inc., State Rd. 909, Km. 1.1, Humacao, P.R. Documents collected during these inspections have been reviewed and compared with documents collected during an inspection of Roche Pharma, Inc., State Rd. 670, Km. 2.7, Manati, P.R. from October 7 to 28, 1996, and with documents submitted to the San Juan District Recall & Emergency Coordinator, including 2 NDA Field Alert Reports and 2 Recall Notifications. Our review of these documents concludes that the product Klonopin® Tablets, 0.5 mg., 1.0 mg. and 2.0 mg. strengths, (NDA 17-533) is adulterated within the meaning of section 501(a)(2)(B) due to the following deviations:

- 1) Failure to provide readily accessible records for the manufacture and packaging of Klonopin® Tablets at the Manati, P.R. facility when requested by FDA [21 CFR 211.180]. In addition, failure to maintain written records so that data can be used for evaluating the quality standards of Klonopin® to determine the need for changes in specifications or manufacturing or control procedures [21 CFR 211.180(e)]. For example:
 - a) Records provided during the inspections indicate that the Manati, P.R. facility manufactured experimental batches of Klonopin® Tablets between October 10, 1996, and February 20, 1997. The lot numbers for of these lots were later changed to commercial lot numbers and the lots were marketed. Of these marketed lots, were either out-of-specification or at the upper limit of specification for individual unknown impurities (including and) at the six month stability station as follows:

Mr. Patrick J. Zenner
July 31, 2000
Page 2

<u>Experimental Batch #</u>	<u>Commercial Lot #</u>	<u>Strength</u>
RJA-25475-001	3101	0.5 mg.
RJA-25475-002	3102	0.5 mg.
RJA-25475-003	3103	0.5 mg.
RJA-25475-004	3104	0.5 mg.
RJA-25475-005	3105	0.5 mg.
RJA-25475-012	3106	0.5 mg.
RJA-25475-013	3107	0.5 mg.
RJA-25475-014	3108	0.5 mg.
RJA-25475-015	3109	0.5 mg.
RJA-25475-020	3114	0.5 mg.
RJA-25475-007	3300	1.0 mg.
RJA-25475-008	3301	1.0 mg.
RJA-25475-009	3302	1.0 mg.
RJA-25475-010	3303	1.0 mg.
RJA-25475-023	3305	1.0 mg.
RJA-25475-024	3306	1.0 mg.
RJA-25475-025	3307	1.0 mg.
RJA-25475-026	3308	1.0 mg.
RJA-25475-027	3500	2.0 mg.

During the inspections of the Humacao facility and by telephone after the inspection, the investigators repeatedly requested information explaining the purpose of these experimental batches. Your firm has failed to provide the Agency with definitive information concerning the manufacture and production of these experimental batches, and the changes implemented for each batch. In addition, we have validation concerns if any of these batches were not manufactured by the approved method.

- b) When records related to the production and control of lots of Klonopin® Tablets manufactured at the Manati, P.R. facility were requested during the 9/99 inspection, the FDA investigator was informed by firm personnel that the records were contained in boxes as shipped from the Manati facility and were not readily available for review.
- 2) Your methods for selecting lots for stability testing do not provide for an adequate number of batches of each drug product as required by 21 CFR 210.166 (b). There were no records provided during the inspections, or in documents submitted to FDA/Center for Drug Evaluation and Research (CDER), that any "round-shape" tablets have been included in the stability testing program. Lots of this product configuration were manufactured until September and October of 1996.

Mr. Patrick J. Zenner
July 31, 2000
Page 3

- 3) Failure to conduct adequate investigations into failures of Klonopin® tablet stability samples to meet specifications for the impurity [redacted] [21 CFR 211.192]. For example:

Additional stability failures were found in other lots of the product, and your firm reported a conclusion that the failures were due to the increased surface area of the "k-shape" tablets. However, no "round-shape" tablets were tested for this impurity until the FDA investigator pointed out during the inspection that this testing had not been done. When a "round-shape" tablet lot was tested, it also failed the specification for impurity [redacted]

- 4) Your firm failed to follow adequate drug product inspection procedures as required by 21 CFR 211.134 in the relabeling of Klonopin® Tablets, Lots # U0003, U0004, U0005, U0501, U0502, U0503, U1002, U1003 and U1004. These lots were manufactured at the Humacao, P.R. facility as commercial lots in anticipation of approval of NDA supplement #032 for change in manufacturing site from the Manati, P.R. to the Humacao, P.R. facility.

On June 28, 1999, you submitted a proposal to FDA to change the expiration date of the product from 36 months to 18 months and to re-label the lots with this expiration date. On August 9, 1999, you submitted a second proposal to FDA to change the expiration date of the product to 12 months. The relabeling of these lots took place at [redacted] in [redacted]. However, after portions of these lots had been distributed, you determined that some of the units had not been re-labeled and had been shipped with the incorrect expiration date, necessitating recall of some of the products. Your firm's investigation into this incident reported that "...employees responsible to plan, design and implement the re-labeling of said Klonopin® lots unintentionally overlooked crucial steps (e.g. clear definition and design of the 200% inspection process) in the inspection process."

- 5) The following stability data for detection of [redacted] (limit = 0.2%) and [redacted] (limit = 0.2%) impurities is a comparison of the information provided in your NDA 17-533 annual reports dated June 12, 1998 and July 14, 1999, and the test results provided in a fax titled "As of May 21, 1997":

<u>Lot #</u>	<u>Stability Station</u>	<u>[redacted]</u>	<u>5/21/97</u>	<u>Fax</u>
3103	3 months	0.1/0.0 %		0.3/0.2 %
3104	6 months	0.2/0.2 %		0.4/0.3 %
			repeat	0.5/0.3 %
3301	6 months	0.1/0.0 %		0.2/0.1 %
3500	6 months	0.0/0.0 %		0.1/0.0 %

This same information is repeated in the submissions made to CDER for changes to lower the expiration date of the product on June 28, 1999, and August 9, 1999. Please clarify why different values for the same test results were reported to the Agency.

- 6) On May 13, 1997, your firm submitted a Field Alert Report to FDA San Juan District reporting out-of-specification results for unspecified impurities in some lots of Klonopin® Tablets. Final submission for this Field Alert Report was made on June 30, 1997. This final submission indicated that the reason for the benzophenone and 4-methyl benzophenone impurities was due to the varnish used in the heat sensitive labels. Our review of the records shows that these two impurities were out-of- specifications in Klonopin® Tablets, 1.0 mg, lot 3300. This lot had a pressure sensitive label and not a heat sensitive label. Please provide information to clarify this finding.

We acknowledge receipt of the response letter, dated July 30, 1999, and signed by Jose M. Venero, for the inspection of the Humacao, P.R. facility from May 10 to July 23, 1999; and of the response letter dated October 19, 1999, signed by Mr. Jose Venero, for the inspection of the Humacao, P.R. facility conducted from September 15 to 29, 1999. With the exception of the issues discussed above, we find the response to adequately address the deficiencies discussed in the FDA-483, Inspectional Observations Form, issued at the conclusion of those inspections.

We recognized that a large portion of the deficiencies discussed in this Warning Letter were not addressed on the FD-483 forms issued at the conclusion of these inspections. The reason for this is that the information was obtained both from documents provided to our investigator during these inspections and from information in our files from an earlier inspection mentioned above and from records submitted by your firm to the FDA.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Current Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District office in writing within 30 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations including an explanation of each step being taken to prevent the recurrence of these or similar violations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Mr. Patrick J. Zenner

July 31, 2000

Page 5

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Wayne Matthews for
Mildred R. Barber
District Director